REMARKS

A. Status of Claims

Claims 1-5, 10-17, 23, 25, 26, 29-35, 38, and 39 are pending in the present application. Claims 1, 13-15, and 23 and are currently amended, and new claims 40 and 41 are presented. The amendments to claims 1 and 13-15 are made to more clearly recite the invention. Claim 14 is also amended to indicate that the fusion polypeptide comprises amino acids 19-134 of SEQ ID NO:1, as discussed below. Claim 15 is also amended to delete subject matter now presented in new claims 40 and 41. Claim 23 is rewritten as an independent claim. These amendments do not add any new matter, raise any new issues, or require any further search, and their entry is respectfully requested.

B. Amendments to the Specification

The specification has been amended to correct clerical and/or typographical errors in paragraphs 51 and 60. No new matter is added by virtue of this amendment, and its entry is respectfully requested. Paragraphs 51 and 60 require amendment for the following reasons. In these paragraphs, the extracellular domain of ActRIIB is defined by reference to amino acids 23-138 of SEQ ID NO:3 or amino acids 19-144 of SEQ ID NO:1. However, the extracellular domain referenced by SEQ ID NO:1 should read amino acids 19-**134** of SEQ ID NO:1 (a 115 amino acid sequence, the same length as amino acids 23-138 of SEQ ID NO:3), not amino acids 19-**144** (which would be a 125 amino acid sequence). Support for this amendment can be found in the attached sequence alignment of the extracellular domains of SEQ ID NO:3 and SEQ ID NO:1. In this alignment, the "Query" sequence is amino acids 23-138 of SEQ ID NO:3 and the "Sbjct" sequence is amino acids 19-134 of SEQ ID NO:1. The unlabeled line between

these two sequences shows residues which are identical in both sequences. This sequence alignment clearly shows that both of these sequences are 115 amino acids long, and that amino acids 23-138 of SEQ ID NO:3 align with amino acids 19-1**34** of SEQ ID NO:1.

Further support for this amendment can be found in the attached article by Garg et al., which was published in 1999 and describes the cloning of a zebrafish ActRIIB. Figure 3 of Garg shows an alignment of deduced amino acid sequences for ActRIIB peptides from various species, including human. As is apparent from Figure 3, the extracellular domain of the deduced human ActRIIB (which immediately precedes the transmembrane domain which is double underlined) terminates at an amino acid, Thr, which is identical to amino acid number 138 of SEQ ID NO: 3 (i.e., Thr), and to amino acid number 134 of SEQ ID NO: 1 (i.e., Thr.). Thus, one of ordinary skill in the art would have known, as of the filing date of the present application, that the extracellular domain of human ActRIIB should be designated as amino acids 19-134 of SEQ ID NO:1, and that reference to amino acids 19-144 of SEQ ID NO: 1 was a typographical error.

C. Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

Claims 1-5, 10-17, 23, and 29-35 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled. The Examiner acknowledges that the specification enables a method for increasing muscle mass via administration of an ActRIIB-Fc fusion protein, or a variant having 95% or more sequence identity to amino acids 23 to 138 of SEQ ID NO:3. However, the Examiner contends that administration of these fusion proteins to an individual with a muscle or neuromuscular disease or disorder is not

enabled by the specification, because applicants allegedly have not used the correct animal model for studying increasing muscle mass in Duchenne's muscular dystrophy (DMD). Therefore, the Examiner alleges that undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

The Examiner has not met his initial burden of establishing a "reasonable basis to question the enablement provided for the claimed invention." M.P.E.P. 2164.04, citing In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Instead, the Examiner merely asserts that "Applicants have not used the right animal model." As explained in the M.P.E.P.,

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. M.P.E.P 2164.04; emphasis added.

The Examiner has provided *no* basis for why the observed effect of the ActRIIB fusion protein would not work in an animal with a muscle disorder such as DMD. Nor has the Examiner provided any reason to doubt the objective truth of the applicants' disclosure. If it is the Examiner's opinion that the claimed method would not work in an animal with a muscle disorder, that basis is simply insufficient. "[I]t is incumbent upon the Patent Office … to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." M.P.E.P. 2164.04, citing In re Marzocchi, 439 F.2d 220, 224 (C.C.P.A. 1971), emphasis added. In the absence of any acceptable evidence or reasoning to back up the bald assertion that the wrong

animal model has been used, the Examiner has not met her burden of establishing a reasonable basis to question the enablement of the claimed invention. For all of the reasons described in detail next, the specification as filed enables the pending claims, which is further confirmed by post-filing experiments in animal models of muscle disorders.

1. The Specification as Filed Enables the Pending Claims

The pending claims are directed to methods for increasing muscle mass in an individual with a disease or disorder in which an increase in muscle mass is desirable. The claims are enabled because the specification discloses methods for using an ActRIIB-Fc fusion protein to increase muscle mass *in vivo*, and provides examples demonstrating that muscle mass is increased *in vivo* by administration of an ActRIIB-Fc fusion protein. The specification discloses use of the ActRIIB-Fc to treat a muscle or neuromuscular disease or disorder, for example at paragraphs 73-74. Although the Examiner has rejected the claims because the specification does not include an example of administering the fusion protein to an animal model of DMD, she has not provided any reason why the skilled artisan would not expect the claimed invention to work as taught.

It is well known in the art that it is desirable to increase muscle mass in individuals with a muscular or neuromuscular disease and/or disorder. Bogdanovich et al., 2002, *Nature*, Vol. 420:418-421 (previously disclosed by applicants on July 19, 2004). As explained in a review article of TGF-β family members, "Myostatin [i.e. GDF-8] is regarded as a good drug target since therapeutics that modulate skeletal muscle growth would be useful for disease conditions such as muscular dystrophy…[S]ince

myostatin blockage is effective for increment of muscle mass even in adults, myostatin blockers are also promising as a treatment for dystrophy." Tsuchida, *Curr. Drug Targets - Immune, Endocrine & Metabolic Disorders* 4:157-166 at 159, 161 (2004) (cited by the Examiner with Office Action of November 9, 2006). These statements make it clear that those of skill in the art believe that muscle disorders such as muscular dystrophy are effected by the GDF-8 pathway. Indeed, inhibition of GDF-8 by blocking antibodies in the *mdx* mouse model of Duchenne muscular dystrophy confirms this therapeutic approach. Bogdanovich et al., 2002. Thus, the skilled artisan would expect inhibition of GDF-8 by an ActRIIB-Fc fusion protein to increase muscle mass in individuals with muscle disorders. Accordingly, the specification, in combination with knowledge of the art, would teach the skilled artisan that administration of an ActRIIB-Fc fusion protein to an individual with a muscular or neuromuscular disease would increase muscle mass.

2. Yaworsky Declaration

In support of the enablement of the pending claims, Applicants enclose the Declaration of Dr. Paul Yaworsky under 37 C.F.R. § 1.132 (Yaworsky Declaration). This declaration presents evidence that administration of an ActRIIB-Fc fusion protein that falls within the scope of the pending claims increases muscle mass in an *in vivo* animal model of muscle atrophy. Applicants respectfully submit that the experiments described in this Declaration were only completed and analyzed in May 2007, and therefore could not have been previously presented. Yaworsky Declaration, ¶ 3.

In this model, muscle atrophy is induced by administration of the glucocorticoid dexamethasone to mice. As described in the Yaworsky Declaration, administration of

dexamethasone *in vivo* results in reduced lean body mass and induces severe atrophy in skeletal muscle. Yaworsky Declaration, ¶ 4. The Yaworsky Declaration further demonstrates that the cross-sectional area of individual muscle fibers is also reduced in this animal model. Id. Therefore, a dexamethasone-treated mouse is an appropriate *in vivo* model of a muscle disease or disorder.

Administration of the ActRIIB-Fc fusion protein increased both muscle mass and muscle fiber cross-sectional area in dexamethasone-treated mice. Yaworsky Declaration, ¶¶ 11, 15. Administration of the ActRIIB-Fc fusion protein also increased the lean body mass of dexamethasone-treated mice. Yaworsky Declaration, ¶ 8. The studies presented in the Yaworsky Declaration clearly demonstrate that administration of an ActRIIB-Fc fusion protein increases muscle mass in an *in vivo* animal model of muscle disease/disorder. Yaworsky Declaration, ¶ 16.

Accordingly, these studies confirm the teaching of the specification, and the claimed invention, namely that administration of an ActRIIB-Fc fusion protein increases muscle mass in an individual with a disease or disorder in which an increase in muscle mass is desirable.

3. Ohsawa et al.

In further support of the enablement of the pending claims, Applicants enclose Ohsawa et al. (*J. Clin. Invest.* 116:2924-2934 (2006)). Applicants note that the reference is not prior art to the present application, but rather provides a post-filing confirmation of the claimed invention. Ohsawa provides further independent evidence that administration of an ActRIIB-Fc fusion protein increases muscle mass in another model of muscle disease.

The muscle atrophy model used in Ohsawa is a murine model of limb-girdle muscular dystrophy 1C (LGMD1C). In this model, mice carrying a dominant negative mutation in the caveolin-3 gene have severe skeletal muscle atrophy and a reduction in the cross-sectional area of individual skeletal muscle fibers. Ohsawa at page 2924 and 2930. Ohsawa demonstrates that injection of ActRIIB-Fc into this mouse strain significantly increases the muscle mass of triceps and quadriceps muscles (compared to injection of PBS). Ohsawa at Figure 6A. Ohsawa also demonstrates that injection of an ActRIIB-Fc fusion protein into this mouse strain increases the cross-sectional fiber size of these muscles. Ohsawa at Figure 6B.

Ohsawa clearly demonstrates that administration of a soluble ActRIIB-Fc fusion polypeptide significantly increases muscle mass in an *in vivo* model of limb-girdle muscular dystrophy, a muscle disease/disorder. These studies again confirm the teaching of the specification, and the claimed invention, namely that administration of an ActRIIB-Fc fusion protein increases muscle mass in an individual with a disease or disorder in which an increase in muscle mass is desirable.

Accordingly, for all of the reasons discussed above, the pending claims are enabled by the specification as filed. Therefore, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be reconsidered and withdrawn.

D. Rejection Under 35 U.S.C. §112, First Paragraph - Written Description

The Examiner also rejects claims 1-5, 10-17, 23, and 29-35 as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The Examiner alleges that the "specification has not shown adequate identifying

characteristics of the claimed genus of degenerative disorders". Office Action, page 6; emphasis added. Applicants disagree for the following reasons.

Applicants respectfully submit that the Examiner's rejection does not apply the correct standard for satisfying the written description requirement. The test for written description is not whether the specification provides "adequate identifying characteristics" of a claimed genus, such as muscle diseases and disorders. Office Action at 6. Rather, the test for written description is whether "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. at § 2163, citing *Lockwood v. American Airlines, Inc.,* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); emphasis added.

In the present case, applicants have described many members of the genus objected to by the Examiner. The disclosure names at least 10 specific muscle or neuromuscular diseases and/or disorders, as claimed. Specification at ¶¶ 15, 74. Exemplary muscle or neuromuscular diseases and disorders to be treated with the ActRIIB-Fc fusion polypeptide include muscular dystrophy, Duchenne's muscular dystrophy, amyotrophic lateral sclerosis, muscle atrophy, organ atrophy, frailty, carpal tunnel syndrome, congestive obstructive pulmonary disease, sarcopenia, cachexia, and other muscle wasting syndromes. Specification at ¶¶ 15, 74. One of skill in the art would be familiar with these disorders, including that they are effected by the GDF-8 pathway. Tsuchida 2004 at 159-161. Thus, the skilled artisan could readily apply this

detailed disclosure of the specification with knowledge of the art to practice the claimed invention.

The written description standard requires that the skilled artisan recognize that Applicants had possession of the claimed invention at the time of filing. M.P.E.P, § 2163, citing Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319 (Fed. Cir. 2003); Vas-Cath, Inc. v. Muhurkar 935 F.2d 1555, 1563 (Fed. Cir. 1991). Applicants' disclosure of ten members of a genus of diseases, considered in view of knowledge in the art, fully supports a method of administering an ActRIIB-Fc fusion protein to increase muscle mass in an individual with a disease or disorder in which an increase in muscle mass is desirable, and satisfies the written description standards articulated by the Federal Circuit in Vas-Cath, Inc. v. Muhurkar. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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